PATENT
Attorney Docket No. 04249.0002-05000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: | |
| SULLIVAN et al. | |
| Serial No.: 08/405,454 | Group Art Unit: 1806 |
| Filed: March 15, 1995 | Examiner: R. Schwadron |
| For: ANTIVENIN COMPOSITION CONTAINING F(ab) FRAGMENTS | |



Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**DECLARATION OF DR. JOHN B. SULLIVAN UNDER 37 C.F.R. § 1.132**

I, **JOHN B. SULLIVAN, M.D.**, hereby declare as follows:

1. I am a citizen of the United States and a resident of Arizona.

2. I received an M.D. degree in 1974, and I am a member of the American Board of Family Practice (since 1978); American Board of Medical Toxicology (since 1980); and American Board of Emergency Medicine (since 1985). My professional training and experience are described below.

Presently, I am the President of Clinical Affairs and Chief Medical Officer at University Physicians, Inc. and University Medical Center in Tucson, Arizona, Associate Dean for Clinical Affairs at the University of Arizona Health Sciences Center, Associate Professor with Tenure in the Section of Emergency Medicine, Department of Surgery, University of Arizona Health

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Sciences Center, and a practicing clinician in medical toxicology and occupational and environmental health.

I was Associate Director of the Rocky Mountain Poison Control Center in Denver, Colorado, from 1978-1984, and in this capacity I was on call 24 hours a day for poisoning emergencies. Many of the emergencies that I treated were the result of snake bites and resulting envenomation. In 1984, Wyeth Laboratories awarded me a research grant for research, development and testing of a purified antibody for snake venom poisoning. In 1986 the Arizona Disease Commission awarded me and Dr. Findlay Russell a grant to study the development and isolation of a human antibody for treating snake venom poisoning.

Throughout my career I have provided clinical care in hundreds of cases of snake envenomation, and have evaluated first-hand the advantages and disadvantages of various methods of treating envenomation. As a result of my experience, I am a nationally recognized expert in the area of venomous snake bites.

I have given many academic and research presentations on the topics of poison management, snake venom poisoning and antivenins, and I have published extensively in these areas. A copy of my Curriculum Vitae and list of publications is attached.

On the basis of my training, my clinical experience, the publication of my work in peer-reviewed journals, my participation in conferences, and my presentation of lectures and seminars in the United States, Canada and Australia, I believe that I am a qualified expert in the areas of snake venom poisoning and treatment thereof.

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3. On information and belief, the Examiner has rejected claims 27, 29, and 37-39 because the invention as claimed allegedly is rendered obvious by Sullivan *et al.* in view of Coulter *et al.* and Smith *et al.* (Office Action dated October 31, 1994.)

4. On May 25, 1995, I attended an interview at the U.S. Patent and Trademark Office with Examiner Schwadron, and Tom Jenkins and Jane Potter, applicants' representatives. At the interview I discussed the background of this invention and I explained why I believe that it would not have been obvious to use F(ab) fragments as treatment *in vivo* of snake envenomation. In this declaration I have repeated and expanded upon the points that I covered during the interview.

5. Those of skill in the art did not expect F(ab) fragments to venom to be useful as antivenins. The development of antivenin production through the years stopped at a final product of $F(ab)_2$'s. For several reasons, it was not obvious that smaller fragments would be clinically efficacious; these reasons are summarized here and discussed more fully below.

(a) F(ab) is cleared more quickly than $F(ab)_2$, antivenin or IgG. Slower clearance of large molecular weight venom proteins was known to be a fact. In humans, venom proteins have a prolonged half life (T1/2) with slow elimination from the body. An F(ab) fragment would be predicted to be totally eliminated within 5 half-lives or 24-26 hours, whereas venom protein requires <u>weeks</u> for elimination. An F(ab) fragment would not increase renal elimination of venom protein since the combined

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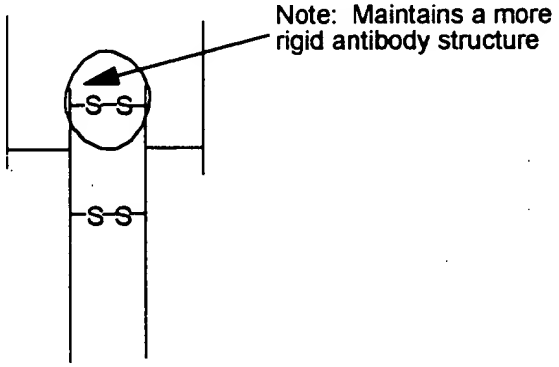
molecular weight of F(ab): protein is greater than the 45,000-50,000 M.W. filtration limit of the kidney. The reticuloendothelial system (RES) and liver are the main organs that eventually clear venom proteins, IgG, and $F(ab)_2$.

(b) Whole IgG and $F(ab)_2$ would "stay around" longer with venom, rendering the proteins essentially nontoxic, or bound up by antibody, until cleared by the RES and liver. The F(ab), with shorter T1/2 and increased renal clearance, would not be available to bind venom. Thus, one would reason, as did the experts at the time, that the use of F(ab) would be relatively or absolutely contraindicated because toxicity might be prolonged and toxin, if redistributed, would be more harmful at other sites in the organism to which a short T1/2 F(ab) would "taxi" and deposit the toxin, leaving it.

6. The early success of equine-derived antivenin containing IgG(T) antibody was due to the nature of the IgG(T) antibody, which has an extra disulfide bond.

an extra disulfide bond in IgG(T)




The extra disulfide bond allows IgG(T) to bind with enhancement to repeating protein antigens. An $F(ab)_2$ of IgG(T) would do the

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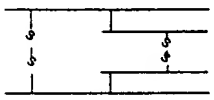
same. An F(ab) would not, thus diminishing clinical efficacy. The nature of the equine IgG(T) has been known for years. This could be obviously reasoned, thus an F(ab) would not be thought to be of clinical value in negating poisoning from venoms.



<--- $F(ab)_2T$ with disulfide bond intact.

My early work with horse antiserum produced an $F(ab)_2T$ fragment. It was obvious that the $F(ab)_2T$ would bind "better" than F(ab) because of considerations discussed above.

7. The molecular weight of F(ab) is about 45,000 daltons. It has a half life that is less than that of $F(ab)_2$. $F(ab)_2$ has a half life similar to that of IgG. The Vd (volume of distribution) of F(ab) is greater than that of $F(ab)_2$, which in turn is greater than that of IgG.

The rapid renal clearance and enhanced elimination of F(ab) was expected to be a detriment to treating clinical envenomations. Thus, thought concerning the art and science of antibody fragments did not indicate the obviousness of F(ab) fragment clinical efficacy. In fact, it was the opposite. In the early 1980's I and others maintained and discussed our concerns that F(ab) would redistribute toxic venom proteins throughout the body, thus producing venom pathology at tissue sites and organ systems not typically seen in patients treated with antivenin or $F(ab)_2$.

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Due to higher Vd and more rapid clearance, the F(ab) was predicted to potentially redistribute and concentrate venom proteins in other organ systems: kidneys, heart, central nervous system, peripheral nervous system, liver, lung and other high blood flow areas.

The F(ab) would "leave" venom at these new tissue sites, "depositing" the poison where it was not previously found. Instead of swelling and local necrosis, there might be coagulopathy, direct cardiotoxicity, liver and kidney damage, potential central nervous system, and peripheral nervous system damage. This could be predicted, and is the reason why others stopped at the $F(ab)_2$ phase. Thus, investigators went no further than $F(ab)_2$ for venom or protein poisoning.

8. Protein (venom) toxicity is reduced by binding of antibody to repeating protein determinants and sterically hindering venom binding to tissue sites. $F(ab)_2$ and IgG have similar ability to preserve the important repetitive binding to determinants. F(ab)'s ability is predicted to be diminished due to their physical nature.

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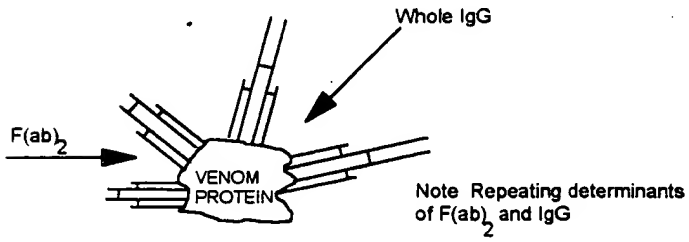
Steric hinderance enhancement by $F(ab)_2$ and IgG.




9. Digoxin and other drugs (non-proteins) have small molecular weights and vary in their clinical pharmacokinetic parameters (T1/2s, Vds, $K_{12}$, $K_{21}$). ($K_{12}$ refers to the rate of distribution of drug to peripheral tissues, where the drug acts on receptors. $K_{21}$ refers to the rate of redistribution from peripheral tissues back to a central compartment, from where the drug is eliminated.) Clinical pharmacokinetic parameters of drugs vary greatly and determine toxicity and clinical pharmacology. Pharmacodynamics also vary greatly among drugs. Anti-digoxin F(ab) is efficacious in digoxin overdose as it would have been predicted to be given the knowledge of digoxin and F(ab)s.

There are examples of F(ab) failure in treating other cases of toxicity. Anti-tricyclic Fab did not work in experimental drug overdose with tricyclic antidepressants. Anti-α-amatoxin Fab increases toxicity.

I and others questioned whether anti-venom F(ab)'s would be effective antivenins. The answer could not be known until experiments and clinical trials were performed.

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10. There are differences between the tissue targets of the toxins discussed above:

- Digoxin has one main target: cardiac tissue.
- Tricyclic antidepressants have several targets, including cardiac tissue and multiple central nervous system sites. Tricyclics also have multiple tissue binding sites.
- Venom has several target tissues.
- α-Amatoxin has several target sites consisting of any cells' nucleus.

F(ab) to digoxin works; Fab to α-amatoxin fails; F(ab) to tricyclic failed in an animal model. Therefore, those of skill in this art predicted that an F(ab) to venom would fail, with the result of increased toxicity due to very little therapeutic efficacy or redistribution of toxin.

11. To summarize, the <u>failure</u> of F(ab) antivenins was predicted for the following reasons:

- F(ab) would cause redistribution of protein toxins to distant, nontargeted sites.
- F(ab) would act as a "taxi" and deposit venom poisons at various organs as it quickly left the body via the kidneys.
- F(ab)'s had failed with other <u>drugs</u> and <u>protein poisons</u> that, like venom, have multiple targets (tricyclics, α-amatoxin), in part because redistribution increased toxicity.

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12. Surprisingly, our results were the opposite from what was predicted:

- F(ab) unexpectedly decreased mortality in early animal studies.
- Clinical studies show that the efficacy of Fab is equal to or greater than $F(ab)_2$ or IgG.
- The effect of F(ab) on decreasing edema was superior to that of $F(ab)_2$.

13. For the foregoing reasons, I, as a qualified expert in the areas of F(ab) antitoxins and treatment of envenomation, believe that it was not obvious to use anti-venin F(ab) to treat snake envenomation. In fact, those of skill in the art expected that F(ab) treatment would fail or <u>increase</u> toxicity of the venom. Such treatment would therefore have been medically unsound and contraindicated.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

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United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

John B. Sullivan, M.D.

Signed on this 25th day of September, 1995

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